Priority effects in microbiome assembly

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Abstract | Advances in next-generation sequencing have enabled the widespread measurement of microbiome composition across systems and over the course of microbiome assembly. Despite substantial progress in understanding the deterministic drivers of community composition, the role of historical contingency remains poorly understood. The establishment of new species in a community can depend on the order and/or timing of their arrival, a phenomenon known as a priority effect. Here, we review the mechanisms of priority effects and evidence for their importance in microbial communities inhabiting a range of environments, including the mammalian gut, the plant phyllosphere and rhizosphere, soil, freshwaters and oceans. We describe approaches for the direct testing and prediction of priority effects in complex microbial communities and illustrate these with re-analysis of publicly available plant and animal microbiome datasets. Finally, we discuss the shared principles that emerge across study systems, focusing on eco-evolutionary dynamics and the importance of scale. Overall, we argue that predicting when and how current community state impacts the success of newly arriving microbial taxa is crucial for the management of microbiomes to sustain ecological function and host health. We conclude by discussing outstanding conceptual and practical challenges that are faced when measuring priority effects in microbiomes.

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Decades of ecological theory and field experiments have demonstrated that the initial assembly of ecological communities or their recovery following disturbance can depend on historical processes, including the sequence in which species arrive[1–5]. Arrival history influences succession when species that arrive earlier alter resources or environmental conditions in ways that impact species that arrive later, affecting their ability to establish in the community. These interactions, known as priority effects, can generate alternative successional trajectories for whole ecosystems[6]. Thus, our knowledge of priority effects in plant and animal communities has critically informed ecological restoration and agricultural practices[7,8].

Until recently, our understanding of historical assembly processes in complex microbial communities has been limited by methodological challenges of characterizing members of microbial communities and their interactions[9]. Now, clear evidence of important priority effects in microbiomes is growing and these effects have been shown to influence microbiome assembly across a variety of habitats, including the mammalian gut[10–13] and skin[14], plant foliage[15–17], nectar[18] and roots[19,20], and free-living terrestrial[21] and aquatic[22,23] communities. As microbiome composition is linked to host health and/or ecosystem function in many of these systems[24,25], priority effects represent an important avenue for the management and manipulation of microbiomes in agriculture, conservation and medicine.

The rich history of research on priority effects in other systems gives microbial ecologists an excellent framework against which to compare and contrast the assembly of microbial communities. However, key differences in scales of observation, community complexity and life history can limit the direct translation of theoretical predictions to microbiomes. To address these challenges, we review known mechanisms and examples of priority effects in microbiomes; discuss when and how the effects of arrival order scale up to differences in microbiome function; describe the experimental and statistical approaches that can identify priority effects in complex, species-rich communities; and, finally, highlight the traits of microorganisms and the environments they inhabit (including their eukaryotic hosts) that influence the likelihood and outcomes of priority effects across systems.

Mechanisms of priority effects

Primary succession (the initial assembly of biota on sterile substrates) and secondary succession (recovery by regrowth and colonization following perturbation) can

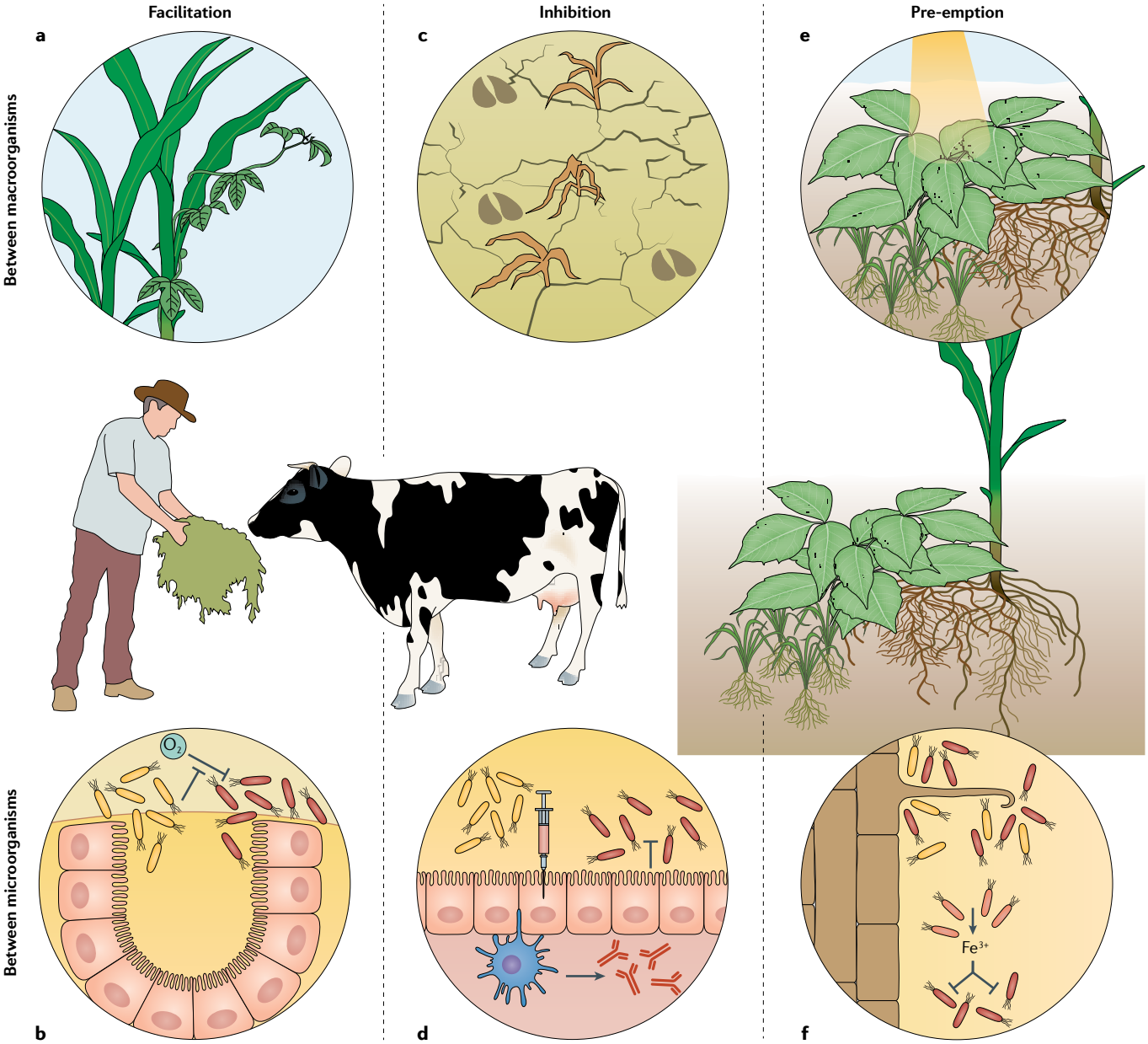


Fig. 1 | **Priority effects between macroorganisms and between members of their microbiomes in a hypothetical terrestrial ecosystem. a** | Early-planted legume crops facilitate overyielding of grains such as corn through nitrogen sparing[124]. **b** | Aerotolerant bacteria facilitate the subsequent colonization of obligate anaerobes in the neonatal intestine by depleting oxygen[49]. **c** | Cattle treading affects soil compaction and water retention, inhibiting the germination and growth of new seedlings[125]. **d** | Early exposure to pathogens confers cross-immunity to related bacteria in many mammals[118]. **e** | Early-arriving plants inhibit the growth of late arrivers through nutrient and light pre-emption[124,126]. **f** | Early-arriving, root-associated bacteria can inhibit late-arriving strains through the pre-emption of essential nutrients such as iron[127].

Priority effects
Refers, in the narrowest sense, to instances in which the outcomes of species interactions vary according to the order of arrival but is often broadened (including here) to include instances in which arrival timing and/or the abundances of resident species affect the ability of new species to establish.

follow multiple trajectories depending on how early colonists affect later arrivers[1] (FIG. 1). Interactions between early-arriving and late-arriving species can be mediated by trophic resources that are actively metabolized, such as limiting nutrients, or by non-trophic resources, such as micro-environments that provide protection from stress. While priority effects are most often detected during initial assembly or recovery periods, they describe effects of resident community composition on arriving species independent of the time since the habitat was created or disturbed.

Niche pre-emption. Niche pre-emption occurs when an early-arriving organism depletes resources, thereby inhibiting the establishment of a late arriver. Multiple lines of evidence point to niche pre-emption, particularly competition for nutrients (exploitative competition), as an important process in microbiome assembly. Within simplified communities of protozoans, bacteria or yeast, early arrivers are often able to exclude late arrivers in microcosms[18,26,27]. Amplicon surveys tracking succession in the *Arabidopsis thaliana* phyllosphere[28] and the infant human gut[29] showed that ecologically similar bacteria

Perturbation
A change in the biotic or abiotic environment that affects organisms in an ecological community; considered a pulse perturbation (or disturbance) when it is brief compared with the population timescales of relevant organisms or a press perturbation (stress, regime shift) if it is more prolonged.

Trophic resources
Any resource that can be metabolized for biomass production.

Non-trophic resources
Any resource that aids the growth or survival of an organism without being consumed for biomass or energy.

Exploitative competition
An adverse indirect interaction between consumers caused by depleting a shared limiting resource.

Interference competition
An adverse direct interaction between species, generally mediated by harmful behaviours or chemicals.

Apparent competition
An adverse indirect interaction between species that increases the abundance or impact of a common enemy (pathogen, consumer, antibody or predator).

tended to occur within the same host population but that individual hosts were dominated by different bacterial species. In the *A. thaliana* study, the spatial arrangement of plants in the greenhouse influenced initial exposure to microbiota members and strains that established early excluded subsequent strains from occupying the same niche[28]. Furthermore, observed priority effects are often strongest among species that require the same resources[18,27]. For example, inoculation order predicted growth among pairs of nectar yeast species with similar amino acid consumption profiles[18]. The life history traits of many microorganisms are not well characterized and may not correlate with marker gene sequences. Thus, approaches in metabolic modelling or metagenomic analyses that incorporate microbial function as well as experimental manipulations of arrival order have proved particularly useful in uncovering these complex effects[10,14].

The effect of nutrient pre-emption may be altered or prevented by the relative concentrations of other limiting nutrients. For example, algae that are individually superior competitors for either silicate or phosphate can coexist or competitively exclude one another, depending on the concentrations of these nutrients in a nutrient-limited freshwater medium[30]. Similarly, competition between bacteria and yeast of the nectar microbiome for amino acids is temperature dependent[31], likely owing, in part, to a shift in the competitors' metabolism. Therefore, broadly speaking, generally inhospitable environments may weaken pre-emptive priority effects in microbial communities by limiting population growth of an early-arriving population and reducing its chances of increasing to a non-invasible density.

Non-trophic resources are also crucial for establishment and thus have the potential to shape priority effects. Niche pre-emption can also occur through competition for space (including through interference competition). For example, ectomycorrhizal fungi compete for space on plant roots[20]. In the mouse gut, early-arriving *Bacteroides* strains penetrate and saturate deep colonic crypts, forcing subsequent strains to occupy less protected niches that are cleared by the mouse immune system[11]. While simple models of competition often predict the success of superior competitors, accounting for niche pre-emption predicts that species can gain an advantage from arriving early despite characteristics that could otherwise limit their competitive fitness.

Niche facilitative modification. Niche facilitative modification (facilitation) occurs when an early-arriving organism alters the environment in a way that benefits a later-arriving organism. Facilitation is also common in microbial communities, where many strains can metabolize byproducts of other organisms. In particular, the ability of arriving microorganisms to establish can depend on the presence of microorganisms that have broken down large organic molecules into smaller molecules, making otherwise inaccessible nutrients available[10,22]. Facilitative priority effects can also be mediated by stress reduction: in harsh environments, such as the plant phyllosphere, arriving strains have a higher probability of survival when they land in multicellular microbial aggregates that have produced extracellular polysaccharides that reduce desiccation stress[32,33]. As in niche pre-emption, the ecological interactions that underlie facilitation often depend on resource availability[34], making it likely that facilitative priority effects can also be highly context dependent.

In host-associated microbiomes, early arrivers can also facilitate late arrivers by modifying host physiology or immunity. For example, some plant-associated bacteria can modify host tissues to increase nutrient leakage[33]. Furthermore, many microorganisms, particularly pathogens, suppress host immunity as they establish, facilitating colonization by other microorganisms that would have otherwise been recognized by the same immune pathway[15,17,35]. Owing to the rapid coevolution of host immune genes and pathogen effectors, the magnitude and direction of this effect can be highly dependent on host and pathogen genotypes. For example, virulent strains of *Xanthomonas perforans* can suppress the tomato immune response and facilitate colonization by *Salmonella enterica*, while avirulent strains of *X. perforans* instead stimulate the immune response and inhibit *S. enterica*[35]. Similarly, prior infection by the fungal pathogen *Zymoseptoria tritici* suppresses the wheat immune response and facilitates *Pseudomonas syringae* colonization, but only in a cultivar that is susceptible to *Z. tritici*. In a resistant cultivar, the opposite occurs: *Z. tritici* infection stimulates the wheat immune response and inhibits subsequent colonization by *P. syringae*[15].

Many microorganisms facilitate the dispersal of other species through substrates or around host tissue. For example, the hyphae of osmotrophic fungi create a physical scaffold and a surrounding micro-aqueous environment that enhances the dispersal of motile bacteria such as *Serratia proteamaculans* in cheese rinds[36]. In such cases, resident strains benefit new arrivers by increasing their access to their environment.

Niche inhibitory modification. Niche inhibitory modification (inhibition) occurs when an early-arriving species modifies conditions (rather than resource levels) in a way that slows or prevents the establishment of later-arriving species[1,6]. Niche inhibitory modification can arise through apparent competition or through interference competition. The best-studied examples of priority effects via apparent competition are mediated by host immunity. Many members of *Bacteroidetes* and *Firmicutes* produce short-chain fatty acids in the human gut that stimulate mucus and epithelial cell growth and production of antimicrobial peptides, reducing subsequent colonization by enteric pathogens[37]. Conversely, pathogens such as *Salmonella enterica* subsp. *enterica* serovar Typhimurium have been shown to modulate host immune responses to inhibit gut commensals and facilitate their own growth[38]. Indeed, although typically considered strictly in terms of molecular interactions with hosts, effector proteins such as Ave1, which is secreted by the fungal plant pathogen *Verticillium dahliae*, can also reduce resident bacterial density in tomato and cotton plants, thus clearing the way for subsequent fungal colonization[39]. Pathogens can also remodel the host environment in other ways, such as through necrosis

of host tissue, which negatively affect the diversity and composition of microorganisms that can survive in the host[40,41]. These effects may help explain the common observation that microbiome diversity is reduced in hosts experiencing disease[24,25].

Apparent competition as a result of shared protozoan or viral predators is likely common in microbiomes and may therefore be an important mechanism by which early-arriving species inhibit subsequent colonization by other species. For example, temperate phages arrive in the microbiome in the genomes of bacterial hosts but can occasionally enter the lytic cycle and infect neighbouring cells, including competitors. The presence of a temperate phage in a resident strain of *Bordetella bronchiseptica* limits colonization by another, phage-sensitive *B. bronchiseptica* strain in pure culture[42]. Apparent competition is likely to influence and complicate priority effects in many other ways, as predation can slow the nutrient depletion or niche construction activities of early-arriving species, select for costly resistance traits and release nutrients sequestered in dormant cells[43]. Increasing evidence indicates that viruses of microorganisms can also interact with eukaryotic hosts; for example, lytic production of a *Pseudomonas aeruginosa* phage increases anti-viral immune responses in the mouse lung, thus suppressing the host response to bacteria[44]. These studies highlight the need for future work to characterize the roles of predation and parasitism in microbiome assembly.

Finally, direct inhibition in host-associated and environmental communities can occur through bacterially produced compounds. In these cases, interference competition can lead to niche inhibitory modification rather than niche pre-emption because the early arriver degrades an environment for a late arriver without necessarily occupying the space itself. In the mouse caecum, acid production by *Bifidobacterium animalis* subsp. *lactis* reduces pH, creating a non-permissive environment for colitis-inducing *Enterobacteriaceae*[45]. In fermented foods, such as cheese and sourdough, *Lactobacillus* and *Lactococcus* species produce bacteriocins with antimicrobial activity against foodborne pathogens such as *Salmonella paratyphi*[46,47]. In the human gut and on human teeth, microaerobic bacteria arrive early in succession and deoxygenate the environment, limiting the establishment of other aerobes while simultaneously facilitating colonization by anaerobes[48,49].

Functional outcomes of priority effects. It is well known that different species can fill similar ecological roles, complicating the interpretation of turnover in community composition across time or space[50]. Functional redundancy, when two different taxa perform similar ecosystem functions (for example, as measured in microbiomes by gene content, chemical productivity or host outcomes) is seemingly common in microbial communities[51,52]. Nonetheless, microbiome assembly history has been shown to affect community-level and ecosystem-level properties, including biomass distribution[53], decomposition rates[21,27], nutrient cycling[21,54,55], host health[14,15,19,56] and productivity–biodiversity relationships[57]. These observations raise the questions of when and how the effects of assembly history are of functional significance.

A helpful framework is to consider species in terms of their resource requirements and environmental impacts (also referred to as guilds or functional groups). Depending on the mechanism, priority effects can occur between species with similar or different resource requirements but are unlikely to affect function when they occur between species from similar functional groups (FIG. 2a,b). However, there are many ways through which priority effects can occur between species with different environmental impacts. Ecologically dissimilar taxa can affect one another by altering resources or environmental conditions, including the abundances of shared predators. Species that differ in most aspects of their requirements and impacts may nevertheless be all limited by an essential resource or, conversely, species with similar requirements may differ in one or a few key genes that translate to different environmental impacts (FIG. 2c–e). The latter case may be especially common in microbial communities, where closely related strains are often distinguished by the presence or absence of entire genes rather than single-nucleotide polymorphisms[58]. An important caveat to this framework is that species-rich microbial communities can contain more taxa that perform unique functions as well as those that are functionally redundant than less diverse microbial communities[59]; thus, the consequences of priority effects for ecosystem function are likely to depend on the community context.

Detecting microbial priority effects

While studies of simplified microbial consortia have been essential for defining the specific mechanisms of priority effects, it is still unclear to what extent these observations apply to either real or complex communities. How common are the various mechanisms of priority effects in natural microbiomes, which taxa do they affect and how do they contribute to community composition as a whole? Here, we consider methods that are used to examine microbiome data with the aim to provide a framework that accommodates the diversity of study systems and sampling regimens in microbiome research.

Synthesizing from multiple approaches. Experimental studies that vary the arrival order of individual strains[16,18,21] or entire consortia[12,23,60] can directly measure both the role of priority effects in community assembly and the importance of external factors, such as nutrient availability, for these effects. Experimental manipulations of phyllosphere and mouse gut microbiome assembly showed that most observed priority effects were inhibitory, with only a minority of strains benefiting from facilitation[12,16]. In the case of the phyllosphere, individual strain manipulations identified a small number of strains (keystone taxa) that were responsible for most observed priority effects[16]. In the mouse gut, priority effects were found to be largely independent of the host immune response, suggesting that direct bacteria–bacteria interactions may comprise the majority of such effects[12]. However, probing the effects

Keystone taxa
A species or strain whose effect is large and disproportionate to its abundance in a community.

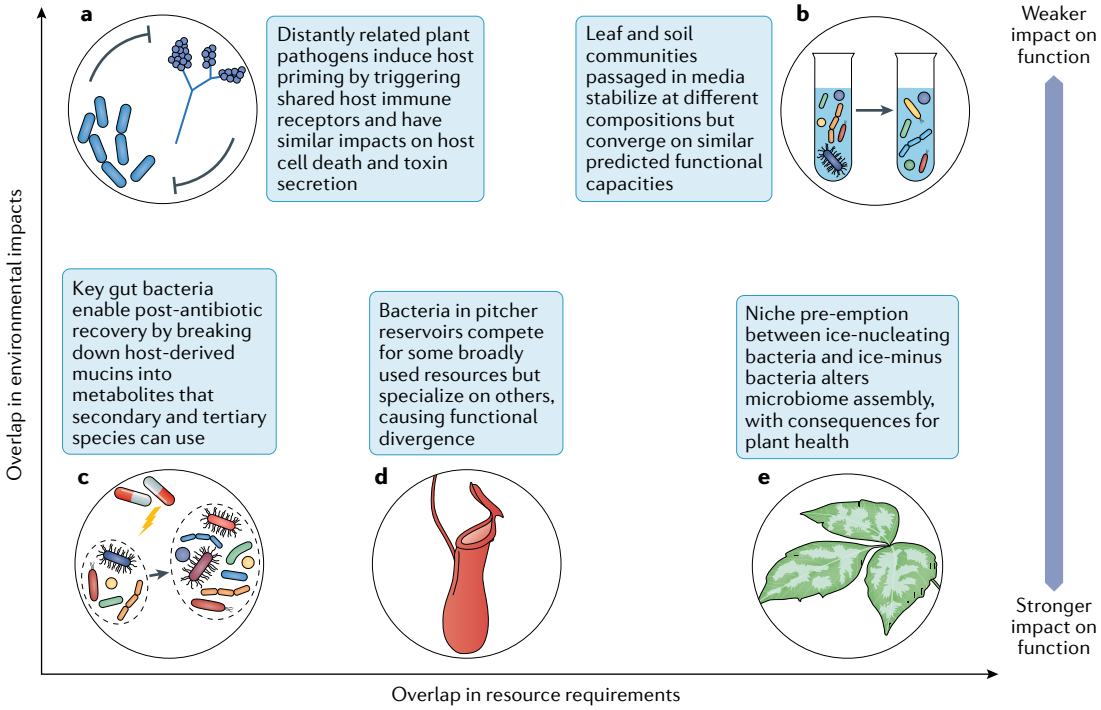
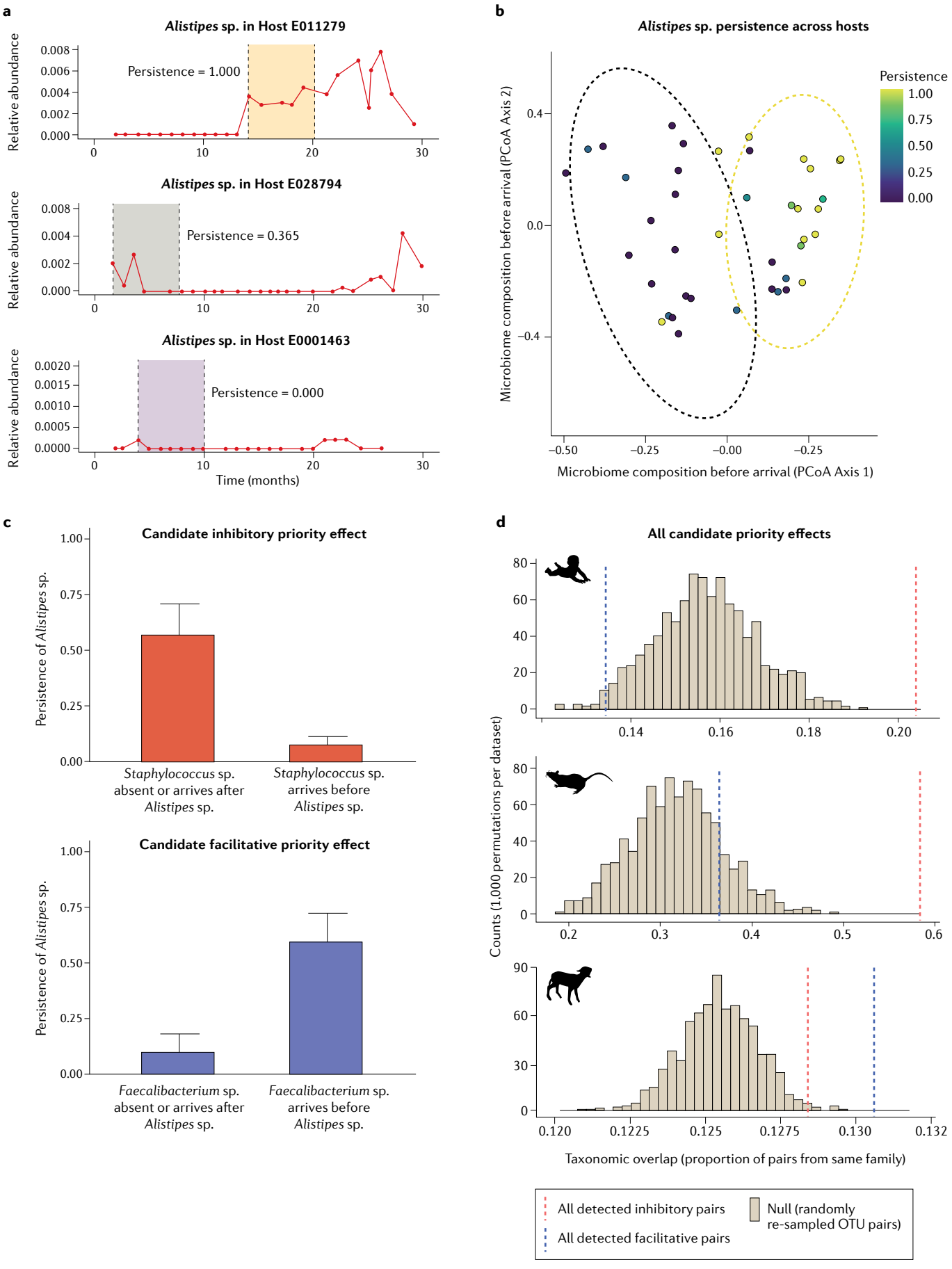


Fig. 2 | **Examples of priority effects with varying impacts on function. a** | Niche inhibitory modification can occur between species with different resource requirements, such as the fungal pathogen *Botrytis cinerea* and the plant pathogen *Pseudomonas syringae*, with similar consequences for host health[128]. **b** | Many instances of priority effects between ecologically similar species do not affect microbiome function[129]. **c** | Niche modification by early arrivers can facilitate or inhibit the colonization of functionally distinct microorganisms, altering the functional trajectory of the community[10]. **d** | Niche pre-emption can occur between ecologically dissimilar species when they compete for a broadly used resource. Serially passaged pitcher plant microbiomes converge on broad functions such as CO_2 respiration despite assembly history but diverge on specialized functions such as endochitinase activity[55]. **e** | Niche pre-emption between microorganisms that require most of the same resources can still affect function when they differ in a few key traits such as the presence or absence of ice-nucleating proteins that cause frost damage in plants[130]. Of note, only aspects of resource requirements and environmental impacts inferred from measurements taken in the case studies cited are depicted to illustrate relationships between assembly history and various functional traits without attempting to summarize all possible components of microbial niches.

of individual strains requires cultivated isolates, whereas only a minority of bacterial species are easily culturable across ecosystems[61]. In several cases, difficult-to-culture organisms have only been grown in co-cultures, relying on other microorganisms for compounds such as amino acids, vitamins or siderophores that they do not produce themselves[62,63]. This extreme metabolic dependence suggests that uncultured taxa are particularly likely to be sensitive to the presence or absence of other taxa during microbiome assembly. In fact, this may contribute to observations of predominantly inhibitory interactions in laboratory studies[16]. As such, despite the clear utility of experimental approaches in probing community assembly mechanisms, measures of priority effects using only culturable strains may miss many interesting or informative cases.

Approaches such as challenging established microbiomes with individual strains to examine invasion success with different resident microbiomes[19,64–66] or, conversely, inoculating hosts with specific isolates and then allowing natural colonization[67], are also experimental but can include naturally diverse communities with currently uncultured taxa. For example, wood disks pre-colonized with individual fungal isolates and deposited in leaf litter for 12 months developed different microbiomes depending on the identity of the pre-colonizer[67]. These approaches are most informative when strains of interest have already been identified but their interactions within their overall community are not known.

Fully observational datasets have the highest potential to capture realistic microbiome dynamics, especially interactions involving rare and/or uncultured taxa, but can be more difficult to interpret in terms of mechanism or causation. Historically, ecologists have taken advantage of natural phenomena such as island formation or major disturbances to determine how communities assemble when successional dynamics are initiated or reset[68,69]. Similarly, microbiome assembly can be measured during initial development of a new host or after disturbances such as antibiotic treatment. Early amplicon surveys showed that infants born by caesarean section acquire a smaller share of their early microbiota from their mothers than infants born by vaginal delivery and signatures of this event persist throughout early life[70,71]. While it is not yet possible to rule out dispersal limitation or environmental differences as contributing mechanisms, recent work attributes some of this variation to niche pre-emption between *Bacteroides* (more abundant


a
Alistipes sp. in Host E011279
Relative abundance
Persistence = 1.000
Alistipes sp. in Host E028794
Persistence = 0.365
Alistipes sp. in Host E0001463
Persistence = 0.000
Time (months)
b
Alistipes sp. persistence across hosts
Persistence
Microbiome composition before arrival (PCoA Axis 2)
Microbiome composition before arrival (PCoA Axis 1)
c
Candidate inhibitory priority effect
Persistence of Alistipes sp.
Staphylococcus sp. absent or arrives after Alistipes sp.
Staphylococcus sp. arrives before Alistipes sp.
Candidate facilitative priority effect
Faecalibacterium sp. absent or arrives after Alistipes sp.
Faecalibacterium sp. arrives before Alistipes sp.
d
All candidate priority effects
Counts (1,000 permutations per dataset)
Taxonomic overlap (proportion of pairs from same family)
All detected inhibitory pairs
All detected facilitative pairs
Null (randomly re-sampled OTU pairs)

◀ Fig. 3 | **Approaches for detecting candidate priority effects in time-series microbiome data. a** | Repeated sampling of individual hosts allows the calculation of arrival times and persistence values for each host–strain combination[13]. Re-analysis of data from infant gut communities sampled monthly for the first 3 years of life[131] revealed variation in persistence of operational taxonomic units (OTUs) among infants. Here, we show the persistence of a representative OTU (OTU17, *Alistipes* sp.) across three infants. Persistence is defined as the proportion of a 6-month period after first arrival (indicated by shaded panels between dashed lines) in which relative abundance was greater than zero. **b** | Variation in the persistence of a single strain across hosts can be associated with resident microbiome composition. Here, we show a principal coordinate analysis (PCoA) in which each point represents microbiome composition immediately prior to the arrival of *Alistipes* sp. (OTU17) in an infant host. Clustering indicates that resident microbiomes associated with high persistence of *Alistipes* sp. were distinct from those associated with low persistence of *Alistipes* sp. Ellipses correspond to 95% confidence intervals based on k-means clustering. **c** | When the persistence of individual taxa after arrival correlates strongly with resident microbiome composition (as shown in part **b**), negative binomial regression[132] can be used to identify microbiome features (that is, individual taxa) that differentiate high-persistence and low-persistence outcomes. Here, we show two taxa identified by this approach that predict persistence of *Alistipes* sp. (OTU17). Error bars represent 95% confidence intervals (1.96 times the standard error of the mean). **d** | We applied the approach described in parts **a**–**c** to published temporal microbiome data for mouse[133], human[131] and cattle[13] intestinal microbiomes within the first 1–3 years of life. In each dataset, the observed phylogenetic structure of the predicted OTU pairs was compared to a null distribution generated by measuring the phylogenetic structure of 1,000 permutations of correspondingly sized samples of OTU pairs from the entire dataset. Across all studies, <10 of 1,000 permutations reached or exceeded the level of taxonomic overlap of OTU pairs predicted to engage in inhibitory priority effects (that is, $p < 0.01$ for all datasets). The taxonomic overlap of facilitative priority effects was also higher than expected by chance in the cattle rumen microbiome ($p < 0.001$) but did not differ from chance in the mouse and human gut microbiomes. Data and code are available at microbiomepriorityeffects. The analysis in this figure is described in greater detail in Supplementary Box 1 and Supplementary Fig. 1.

in vaginally born infants) and *Bifidobacterium* strains (more abundant in infants born by caesarean section). Whichever of these two genera was most abundant contributed the most to human milk oligosaccharide breakdown in the infant gut[29]. Observational studies have also revealed that the compositional trajectory of the human gut microbiome after antibiotic perturbation depends on the activities of certain bacteria. Across several human cohorts, taxa associated with antibiotic recovery had genomes enriched for carbohydrate-degrading enzymes, particularly those that degrade host-derived mucins[10]. This observation suggests that the initial breakdown of host-derived metabolites can support the growth of secondary or tertiary species (niche facilitative modification) and pave the way to the recovery of pre-antibiotic diversity.

Identifying taxa for further study. Experimental manipulation of arrival order allows direct examination of causative effects, an important and difficult undertaking in complex ecological communities. However, in the absence of a priori hypotheses about which taxa are expected to interact, searching for a 'needle in the haystack' by individually permuting all strains in a model community can quickly become prohibitively labour intensive. With an appropriate observational dataset, it is possible to statistically predict which taxa are of interest and narrow the search space for subsequent experimental validation. Through re-analysis of publicly available data from the succession of human, mouse and cattle intestinal microbiomes, we demonstrate one way in which this can be done. Repeatedly sampling hosts over time captures the arrival times and subsequent persistence of individual taxa (FIG. 3a). With sufficient cohort size, the variation in persistence of individual taxa may be linked to resident microbiome composition before their arrival (FIG. 3b,c). Across datasets, candidate inhibitory priority effects consistently occurred among more closely related taxa than expected by chance (FIG. 3d). This pattern mirrors experimental work in aquatic microcosms[27], nectar yeast communities[18] and probiotic clinical trials[64], in which resident strains limited the subsequent establishment of other, closely related strains.

In many cases, repeated profiling of the same community can be challenging to perform, either as a result of destructive sampling, spatial structure within the microbiome or difficulty in acquiring samples from the same individual hosts over time. When working in a system that does not permit temporal sampling, it is best to draw from a large population of hosts sampled at different times with high temporal resolution. For example, the development of the rice root microbiome was followed by destructively sampling plants weekly or bi-weekly until maturity and senescence, using four plant genotypes unequally grown in field trials at three separate field sites[72]. In these high-resolution datasets, strains of interest can be identified by linking the abundance, rather than the persistence, of individual taxa to the composition of the remaining community (FIG. 4a) and then to individual strains therein (FIG. 4b). Using this information, it is then possible to design complementary laboratory experiments to explicitly test for priority effects involving the identified strains. In general, it is often necessary to integrate multiple pieces of evidence, including mathematical predictions, field observations and laboratory experiments, to fully understand ecological assembly processes in complex systems[73].

Shared insights across systems

Sufficient theory and data are now available to address the characteristics of priority effects across systems. Although individual priority effects and their underlying mechanisms are likely to be system specific, we can begin to identify general circumstances that affect the likelihood and outcomes of priority effects. Mathematical models have an important role here as they allow the manipulation of parameters that vary across systems (such as resource availability[30], dispersal rates[74], spatial structure[75] and metacommunity structure[76]). Such insights will allow us to move towards a more predictive science and help to determine which principles apply both in communities of microorganisms and those of macroorganisms.

Population dynamics. Priority effects are shaped by numerous properties of microbial populations, many of which are likely to interact (TABLE 1). Large populations or individual sizes of early arrivers commonly strengthen priority effects through niche pre-emption as they deplete resources, including space, more rapidly[77–79]. Population density can be especially important in habitats with only a few favourable microenvironments such as colonic crypts in the mammalian gut[11] and stomata

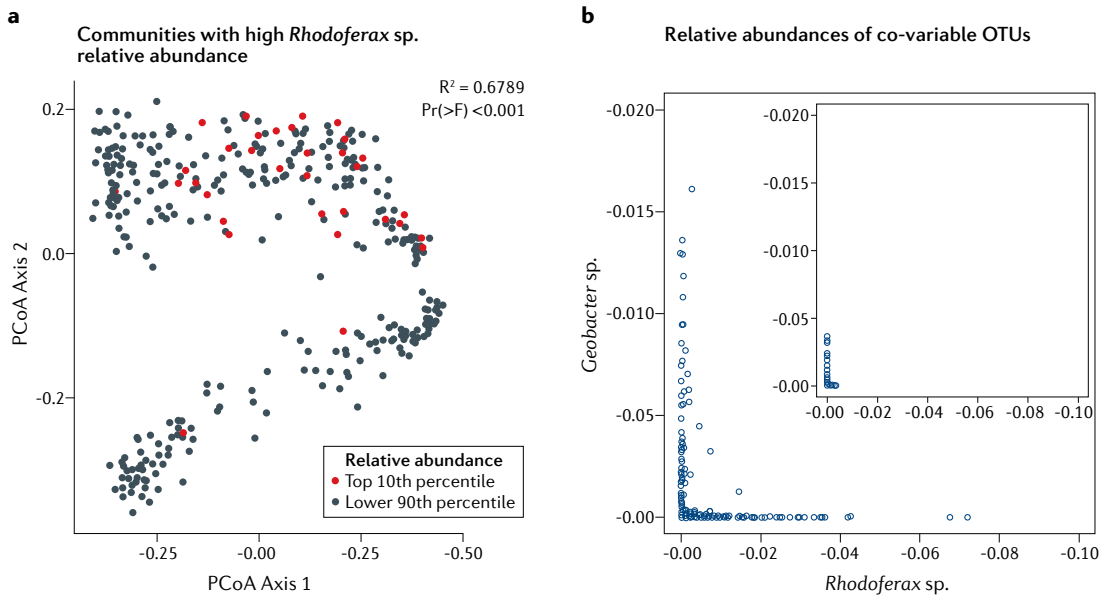


Fig. 4 | **Identifying strains of interest in destructively sampled microbiome data. a** | Destructive sampling of plant hosts over the course of their development allows the identification of strains whose abundance correlates with altered community states. Rice root endosphere samples from three field trials were harvested at common, bi-weekly time points from host germination to senescence[72]. In our re-analysis of this published data, nested ANOVA reveals operational taxonomic units (OTUs; such as *Rhodoferax* sp.) whose abundance is significantly correlated with altered community states (R^2 and *p* value of the F statistic (Pr(>F)), top right) despite a predominant effect of host age at sampling. **b** | Co-variance of OTUs reveals candidates potentially involved in niche pre-emption. For example, *Rhodoferax* sp. from part **a** co-varies with several OTUs annotated as *Geobacter* spp. across time points as well as at late time points at which *Geobacter* is predicted to be more fit in this system (for example, at 112 days; inset). That is, the presence of *Rhodoferax* sp. precludes *Geobacter* spp. and vice versa. The analysis in this figure is described in greater detail in Supplementary Box 2 and Supplementary Fig. 2. PCoA, principal coordinate analysis.

on leaf surfaces[80]. The impact of niche modification can also depend on density. Nurse tree canopies in plants[81] and cellular aggregates in bacteria[82] both shield immigrating individuals from heat and ultraviolet stress, with denser populations being more protective. Low to intermediate densities of fermentative bacteria facilitate the growth of photoheterotrophic bacteria but large populations overproduce organic acids, acidifying the environment and changing the interaction from facilitative to inhibitory[83,84]. Ectomycorrhizal fungi can facilitate Pinaceae invasion into new environments but only when they are present in high densities[85]. Last, host immune modification typically requires sufficient biomass for detection. For example, activation of the plant immunoreceptor FLS2 depends on the dosage of microbial flagellin[86]. Similarly, the tolerance of the host mosquito species *Aedes aegypti* and *Aedes albopictus* to Dengue virus conferred by the endosymbiotic bacteria *Wolbachia* depends on the density of *Wolbachia*[87].

However, not all priority effects are influenced by population density. In many cases, the impacts of the early arriver and the requirements of the late arriver are better predictors of community assembly outcomes than abundance[88]. For example, larger phototrophs that use light less efficiently coexist with smaller, more efficient taxa that are less impacted by shading in both terrestrial plant assemblages[89] and microbial communities[90,91]. In other cases, small populations of keystone species can, despite their rarity, substantially impact subsequent microbiome colonization[92,93]. One such species is the bacterium *Porphyromonas gingivalis*, a low-abundance member of dental biofilms that can alter oral microbiome composition and cause inflammatory disease[92].

Spatial and temporal scales. The study of priority effects requires a priori understanding of both the spatial and temporal scales of community assembly. Unlike well-mixed liquid lab media, most habitats are physically and chemically heterogeneous. Priority effects among microorganisms therefore depend not only on population density but also on the distribution of individuals in space. Environmental features such as fluid velocity gradients[94], soil granularity[95] and the distribution of free water on surfaces[96] all affect spatial patterns in microbial communities. Although the influence of spatial structure on priority effects in microbiomes has not been well studied, several predictions can be generated from theory and data on contemporaneous strain interactions. Physically structured environments allow individuals to associate more often and more predictably with kin or mutualistic partners and such spatial associations are widely believed to stabilize cooperative traits by excluding non-contributors[97,98]. Priority effects that are mediated by metabolites[10,22] may therefore be more pronounced in spatially structured environments, where these products can be retained locally ('privatized') by the partners or consortium. Conversely, theoretical analyses and experiments show that spatial structure can allow competitors

Metacommunity
A set of interacting communities that are linked by dispersal.

Community coalescence
The mixing of multiple ecological communities.

to stably coexist over larger spatial scales by occupying different microhabitats[75,99]. Early-arriving strains should be slower to saturate all available microhabitats in highly structured environments, weakening their ability to pre-empt late arrivers. Moreover, depending on whether dispersal to nearby microhabitats is more likely from within the metacommunity or from without, arrival times to microhabitats will vary among strains, blurring the overall patterns of priority effects observed.

Spatial scales of priority effects depend on their underlying mechanisms as well as on properties of the environment (FIG. 5a–c). Many interactions among microorganisms are mediated by secreted compounds, such as metabolites, toxins and enzymes, that are often highly restricted in range[100]. Advection (transport of a substance by flow of a fluid) and diffusion are limited by extracellular polysaccharides in biofilms but can occur over longer distances in many settings depending on viscosity and flow in fluids or on porosity and permeability in solid substrates (such as soils, sediments, leaf surfaces and skin). Moreover, in cases where interactions are modulated by host immunity, these effects can be far-reaching relative to cell or aggregate size[15,101].

As with spatial distances, the temporal windows across which microorganisms interact can depend on several factors, including host biology (FIG. 5d–f). Microbial populations present in reproductive organs (for example, vaginal and floral populations) can populate offspring and shape microbial succession across host generations[71,102]. Similarly, strains that colonize during critical periods of host immune system development can shape antigen recognition within and across host generations[103,104]. Of note, modification of host immunity may be unusual in that, once it has occurred, it may continue to impact community composition regardless of the continued presence or abundance of a causative organism in the community[103].

In many cases, the strength of priority effects increases with the lag time between early and late arrivers[12,23]. Given sufficient lag time, priority effects can also be the result of evolution. Though often overlooked, early arrivers may not only pre-empt and monopolize resources but also have more time to adapt to local conditions and/or to diversify (BOX 1). Given the potential for long-term changes in fitness in resident species, we might expect priority effects in microbial communities to be longer-lasting (when scaled to generation time) than in their plant and animal counterparts and to involve eco-evolutionary interactions more often.

Dispersal and coalescence. An unusual feature of microbial habitats, especially in host-associated systems, is the frequent appearance of pristine or nearly pristine substrates. Both newborn animals and newly emerged seedling hosts are generally sterile or have limited microbial colonization and events such as wounding can make previously microorganism-free host tissue available for colonization within the lifetime of a host. In periods of primary succession, stochastic processes such as birth, death and immigration tend to have a stronger role than later on[13,28,72]. These processes may balance or even overwhelm deterministic processes, such as host age, environmental variation or the niche pre-emption and modification processes described in this Review[105].

Another unusual feature of microbiomes compared with plant and animal communities is the frequent occurrence of community coalescence[106] in microbiomes, such as through mixing of freshwater and marine habitats

Table 1 | **Importance of population- and community-level parameters in priority effects**

Parameter	Niche pre-emption	Local adaptation
Dispersal rate of early arriver	High dispersal rates increase chances of colonizing empty habitats and pre-empting resources[23]	High continuous dispersal can diminish rates of local adaptation of established colonists[74]
Lag time between early and late arrivers	The strength of priority effects should scale with lag time until the early-arriving population reaches carrying capacity[23]	The strength of priority effects should scale with lag time for much longer as evolutionary changes occur in the early-arriving population[120]
Fitness difference between early and late arrivers	Large fitness differences (i.e. late arriver is a superior competitor) may supersede priority effects[6]	Initial fitness differences should be less important, given sufficient time for early arrivers to adapt[121]
Initial size of early-arriving populations	Large initial population sizes buffer against ecological stochasticity and reduce the time needed to effect change on the environment[78]	Large initial population sizes buffer against ecological stochasticity and genetic drift[120]
Mutation rate in early-arriving populations	Unknown	High mutation rates facilitate adaptation to the new environment[120]
Standing genetic variation in early-arriving populations	Unknown	High standing variation facilitates adaptation to the new environment, especially in cases of short lag time between early and late arrivers[120]
Diversity of early-arriving community	May increase niche construction and favour subsequent diversification (including establishment of late-arriving populations) but with diminishing returns as niches are saturated[122]	Adaptation of individual populations can be limited by the presence of other community members, particularly competitors[123]

or through close contact between hosts. For example, the skin microbiota of members of opposing teams in roller derby (a high-contact sport) converged during a game[107]. In such cases, the resident community will likely have an advantage over the arriving community, but what remains unclear is how much of the observed priority effects at the whole-community scale are the result of individual strain-level effects versus outcomes of community interactions. Experiments that manipulate the dispersal timing of entire communities[23,60], alongside detailed characterizations of pairwise interactions, will reveal whether the traditional concept of priority effects should be expanded to include emergent effects that cannot be captured by pairwise interactions between resident and arriving strains.

Finally, although in this Review we have largely focused on how the resident microbiota affect the persistence of new species once they arrive, it may be possible for residents to influence which species arrive to the community in the first place. For example, recent work on floral microbiomes shows that animal pollinators mediate microbial dispersal to flowers and that epiphytic floral microorganisms can in turn alter nectar chemistry and influence future pollinator visits[108]. Whether nectar microorganisms can cause priority effects by influencing pollinator recruitment remains to be tested.

Conclusions and outlook

Laboratory experiments and field surveys point to priority effects as key, understudied determinants of microbiome assembly and function. Widely used approaches to measuring priority effects each have their associated merits and challenges. Experimental approaches are limited by microbial cultivability and niche predictions, while field-based approaches are limited by the difficulties of repeatedly sampling the same individual host or environment without altering the community. The development and integration of single-cell and multi-omic sequencing technologies[109], imaging mass spectrometry[110], quantitative stable isotope probing[111] and high-resolution cellular imaging techniques[112] will help to answer questions that are beyond the reach of

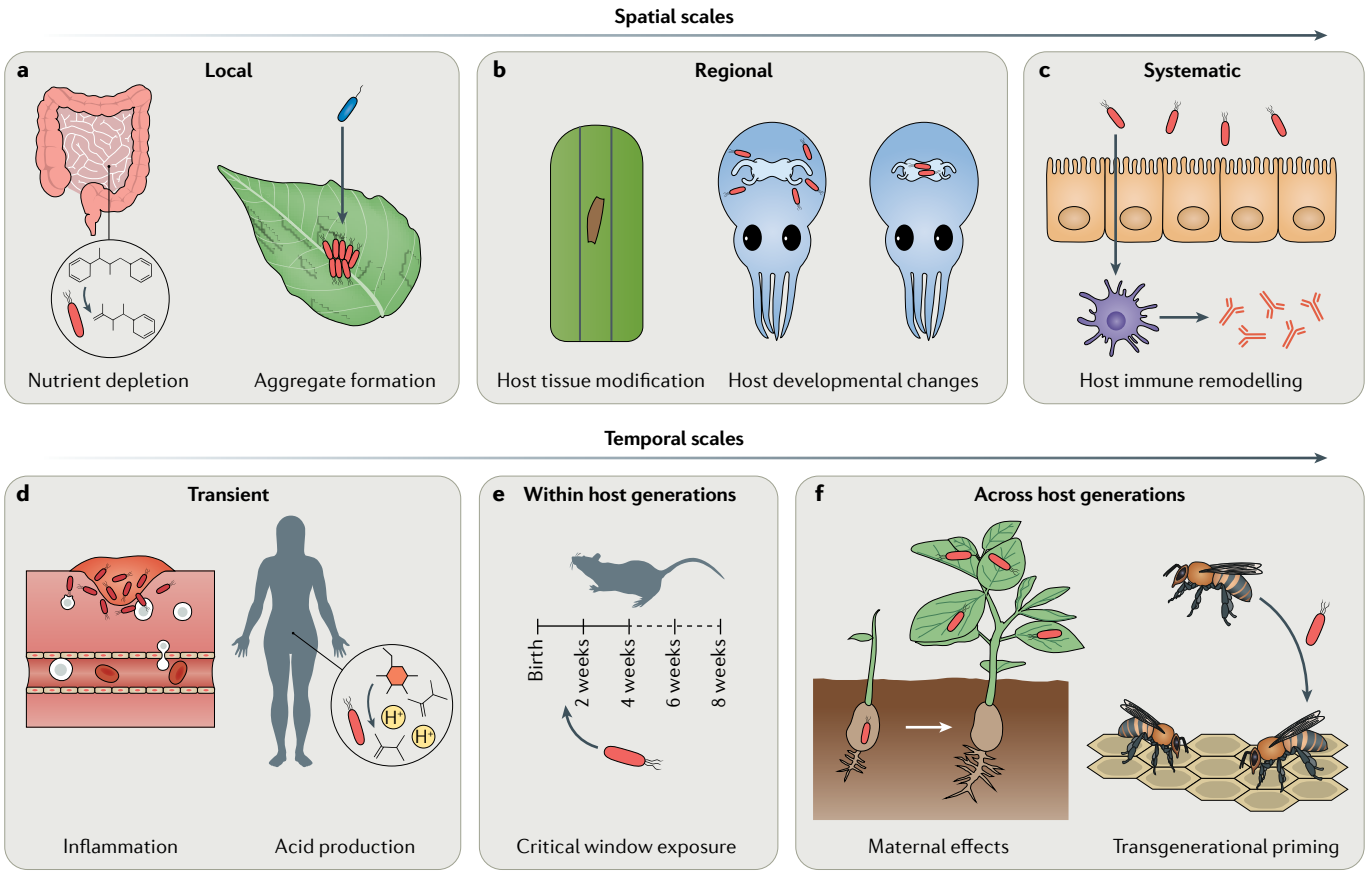


Fig. 5 | **Priority effects act on a range of spatial and temporal scales.** **a** | Early-arriving microorganisms can alter the local environment in many ways, such as by depleting nutrients or producing extracellular polymeric substances that protect other cells from desiccation[33]. **b** | Microorganisms can interact indirectly at greater distances by modifying a shared host organ. Microbial necrosis of plant tissue reduces subsequent microbiome diversity, favouring a minority of taxa that can metabolize diseased tissue[40,41]. Bacteria in seawater stimulate Hawaiian bobtail squids to harvest *Vibrio fischeri* symbionts, which trigger the developmental changes that exclude non-symbionts from the squid ocular crypts[134]. **c** | Modification of host immune pathways can affect microbial colonization in other host tissues such as between intestinal and lung microbiota[101]. **d** | Microorganisms can produce short-term, reversible changes to the host environment, such as transient immune responses or changes in pH in the vaginal microbiome. For example, *Lactobacillus* spp. promote an acidic environment that reduces the colonization success of many common vaginal pathogens[135]. **e** | Microbiota exposure within a 'critical window' after birth can permanently shape adaptive immune responses[103]. **f** | Microorganisms that colonize hosts can be directly transmitted to offspring[102] or induce heritable changes in immune signalling[104], thereby shaping succession of the offspring microbiome in both cases.

Box 1 | **Evolutionary mechanisms of priority effects**

In natural adaptive radiations, community assembly experiments and models, local adaptation and diversification by early arrivers has been shown to limit subsequent colonization by other species[74,120,136]. Priority effects through local adaptation are predicted to be most common when nearby habitats are similar enough that immigrants can survive, but different enough that early arrivers can realize fitness gains over time[120]. By contrast, priority effects through diversification depends largely on the heterogeneity of the environment and may feedback to further increase environmental heterogeneity[137].

Most known examples of evolutionary priority effects are inhibitory (that is, early arrivers reduce the success of late arrivers), although some exceptions exist. For example, *Daphnia magna* populations that coevolve with predatory fish occupy deeper and darker water layers, freeing up the shallows for late-arriving zooplankton species[136]. In general, coevolution with predators or parasites often entails fitness costs associated with counter-defences[138], and these adaptations can reduce the competitive ability of early arrivers. Extended coevolution could also cause parasites to specialize on early-arriving strains, making later-arriving strains less susceptible and encouraging community turnover[139].

Despite the mounting evidence for evolutionary priority effects in model microbial systems discussed above, it is unclear how microbial dispersal shapes either the lag time between or standing genetic variation within populations of arriving species in most microbiomes. Our understanding of these factors in natural communities remains limited by the difficulties of tracking strain-level variation in metagenomes. However, recent work in the human gut suggests that the local adaptation of resident microorganisms may limit invasion by new strains. Within 6-month intervals, genetic turnover within metagenomes was largely attributed to selective sweeps within resident populations rather than to replacement by new strains[113]. A powerful future approach will thus be to integrate metagenome-based lineage tracking with strain isolation and fitness measurements in the laboratory.

Ecological character displacement
Evolutionary divergence of species with overlapping ranges to lessen resource competition.

amplicon sequence analyses alone but must still be performed in ways that reflect or reveal the known spatial and temporal scales of priority effects. For example, pairing amplicon and metagenome sequencing provides complementary views of the taxonomic and functional features of the resident microbiome that affect the establishment of new arrivals[64] as well as the functional consequences of priority effects[10]. Lineage tracking within metagenomes over time[113] will help to identify priority effects between closely related strains. Given that niche pre-emption is often strongest among closely related taxa[18,27,64] (FIG. 3), strain-level analyses are likely to uncover many unknown examples of priority effects. Lastly, paired analyses of microbiome dynamics and host metabolomics will shed light on niche modification activities by the resident microbiota[15].

Our current knowledge of priority effects focuses largely on ecological interactions that affect resource availability or stress reduction. However, predation and parasitism are also known to shape community assembly outcomes[114]. Multi-kingdom surveys of microbial community succession are becoming more common[115] and, as more are undertaken, they will reveal how assembly history shapes rich, complex environments.

When microbial strains consistently coexist and interact over many generations, these interactions have the potential to coevolve. The coevolution of competitors often leads to ecological character displacement[116] as has been observed in *Pseudomonas fluorescens* populations in microcosms[117]. Of course, host-associated microorganisms are unusual in that the environment they inhabit is engaged in ecological and evolutionary processes of its own. How the contrasting timescales of host evolution and the evolution of host-associated microbiota interact to shape priority effects remains to be determined but clues might be gleaned from the study of 'critical windows' in immune recognition across host species[118].

Overall, the existing data make it clear that priority effects shape microbiome assembly and stability. However, the complexity of these systems and the challenges of moving from co-abundance patterns to ecological interactions and functional processes still limit our ability to predict how and when these effects will occur. Among the open questions are: how long-lasting are priority effects? What are the typical spatial and temporal distances over which they occur? And, do our existing ecological models need to be reconsidered in light of differences between microorganisms and macroorganisms? Addressing these questions will be key if we are to leverage our understanding of priority effects to engineer or manipulate microbiomes, for example, by creating disease-suppressive communities or probiotics. Recent evidence that the establishment of probiotic strains can hinder the recovery of gut microbiome diversity[119] highlights the potential problems that can occur if priority effects are not considered as we begin reshaping microbiomes for human, livestock, crop and environmental health.

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